The Effect of Lavender Oil on Perioperative Pain, Anxiety, Depression, and Sleep after Microvascular Breast Reconstruction: A Prospective, Single-Blinded, Randomized, Controlled Trial

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Abstract

Background Psychosocial distress, depression, or anxiety can occur in up to 50% of women after a breast cancer diagnosis and mastectomy. The purpose of this study was to assess the potential benefit of lavender oil as a perioperative adjunct to improve anxiety, depression, pain, and sleep in women undergoing microvascular breast reconstruction.

Methods This was a prospective, single-blinded, randomized, controlled trial of 49 patients undergoing microvascular breast reconstruction. Patients were randomized to receive lavender oil or placebo (coconut oil) throughout their hospitalization. The effect of lavender oil on perioperative stress, anxiety, depression, sleep, and pain was measured using the hospital anxiety and depression scale, Richards–Campbell Sleep Questionnaire, and the visual analogue scale.

Results Twenty-seven patients were assigned to the lavender group and 22 patients were assigned to the control group. No significant differences were seen in the perioperative setting between the groups with regard to anxiety ($p = 0.82$), depression ($p = 0.21$), sleep ($p = 0.86$), or pain ($p = 0.30$) scores. No adverse events (i.e., allergic reaction) were captured, and no significant differences in surgery-related complications were observed. When evaluating the entire cohort, postoperative anxiety scores were significantly lower than preoperative scores ($p < 0.001$), while depression scores were significantly higher postoperatively as compared with preoperatively ($p = 0.005$).

Conclusion In the setting of microvascular breast reconstruction, lavender oil and aromatherapy had no significant adverse events or complications; however, there were no measurable advantages pertaining to metrics of depression, anxiety, sleep, or pain as compared with the control group.

Keywords
- breast reconstruction
- aromatherapy
- reconstruction
- breast cancer
- lavender

Up to 50% of women may experience psychosocial distress, depression, and anxiety following a cancer diagnoses and mastectomy.[1–5] Despite the potential for breast reconstruction to mitigate cancer-related distress, a sizable portion of patients experience anxiety and depression in the acute perioperative period after reconstructive surgery.[1,4,5]

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Recently, there has been increased emphasis on implementing enhanced recovery after surgery (ERAS) protocols to reduce the number of opioid analgesics and anxiolytics prescribed to patients who undergo microvascular breast reconstruction.[6,7] This is necessary to not only reduce risk factors, such as overdose and respiratory distress, but to also reduce the incidence of comorbid psychological conditions (i.e., anxiety and depression) that often present in the patients with breast cancer diagnoses.[8–10] Thus, further investigations into low-risk therapeutics that relieve perioperative pain, anxiety, and depression are warranted.

Previous studies have demonstrated the benefits of aromatherapy with essential oils to benefit patients' mood and health.[11–13] Specifically, lavender oil is composed of chemical constituents, linalool, and linalyl acetate that have been suggested to have anxiolytic effects through the inhibition of the GABA(A) binding receptor in the central nervous system.[14,15] Studies examining these effects in the surgical patient have presented conflicting evidence and are largely hindered by inadequate study design and poor methodology.[12,13,16–18] Furthermore, no studies have examined the benefits of aromatherapy in breast cancer patients who undergo microvascular breast reconstruction. The aim of this study was to assess the potential benefit of lavender oil as a perioperative adjunct to mitigate anxiety, depression, pain, and improve sleep in women undergoing microvascular breast reconstruction.

Methods

This was a prospective, single-blinded, randomized controlled trial designed to evaluate the use of lavender oil to reduce perioperative anxiety, depression, pain, and improve sleep in patients who undergoing microvascular breast reconstruction. Procedures were performed by three surgeons at a single surgery center between December 2017 and January 2020. The trial was approved by the Institutional Review Board at Duke University Medical Center. The study sponsor, dōTERRA International, provided the essential oils that were used in this study.

Patients

Adult female patients' ages 18 to 85 years who were previously diagnosed with breast cancer and undergoing microvascular breast reconstruction were eligible for this study. Patients were excluded if they were pregnant, did not carry a breast cancer diagnosis, or had a history of sensitivity to lavender oil or any of its ingredients.

Study Design

After meeting all eligibility criteria, a total of 58 patients (29 in the experimental group and 29 in the control group) were enrolled in this study (►**Fig. 1**). This was a prospective, single-blinded, randomized controlled trial with a 1:1 treatment allocation of patients placed in two parallel groups: (1) patients who received lavender oil and (2) the control group who received coconut oil. Fractionated coconut oil was selected as the control substance due to its colorless, odorless, and inert nature. A randomized block design with study arm allocation known only to the study coordinator until the day before surgery was used for randomization.

Beginning in the preoperative holding area, patients had four drops of lavender or coconut oil placed on their left and right wrists. The patients were then instructed to rub their wrists and hands together and then inhale and exhale slowly for 1 minute. Intraoperatively, the anesthesia team applied four drops of lavender or coconut oil on the patient's temple at every 2 hours until completion of the surgery. Postoperatively, nurses were instructed to administer the lavender or coconut oil to patients at every 4 hours in the same manner as previously described between the hours of 6:00 a.m. and

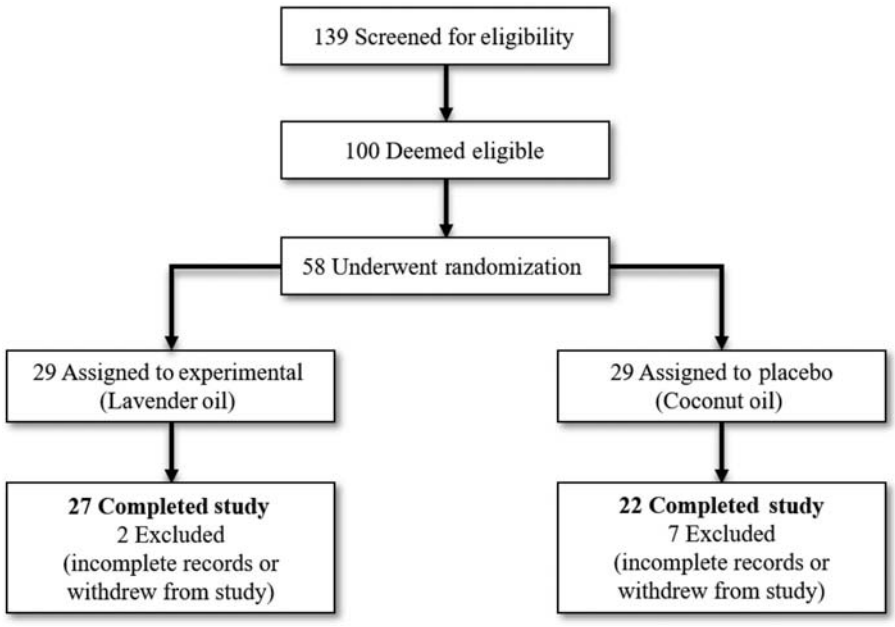

Fig. 1 Patient enrollment.

6:00 p.m. Between 6:00 p.m. and 6:00 a.m., the essential oil was applied to a cotton ball that was placed within 20 cm of the patient. This method of administration was adapted from previous studies that examined the benefits of essential oils on perioperative anxiety and nausea and vomiting.[19,20] Blood pressure, pulse rate, and respiratory rate were monitored in the intraoperative and postoperative period approximately 30 minutes after the administration of the essential oil. The scales used to measure patient pain, sleep quality, anxiety, and depression were administered to patients in the preoperative holding area and then every postoperative day (POD) throughout the patient's hospitalization.

Postoperative Care

All patients were managed postoperatively according to previously published ERAS pathways for patients undergoing microvascular breast reconstruction.[21,22] Briefly, patients receive multimodal pain management beginning in preoperative holding that consists of acetaminophen, gabapentin, celecoxib, naproxen, oxycontin, and a scopolamine patch. Intraoperatively, patients receive ketamine boluses in addition to fentanyl and transversus abdominis plane blocks with liposomal bupivacaine. Postoperatively, pain management regimens consist of nonopioid medications (e.g., acetaminophen, celecoxib, and gabapentin) with oral opioids available for breakthrough pain. On POD1, patients are encouraged to get out of bed to the hospital chair and ambulate with assistance beginning on POD2. Patients are typically discharged from the hospital on POD3 or POD4.

Data Collection and Outcome Measures

Baseline patient demographic and clinical variables included age, body mass index (BMI), race, smoking status, medical comorbidities, psychiatric history, oncologic breast history (e.g., breast cancer type and hormone receptor status), breast surgery history, receipt of adjuvant or neoadjuvant chemo/radiation therapy, and receipt of hormonal therapy. Reconstructive variables included timing of breast reconstruction, laterality, and type of microvascular breast reconstruction. Surgical complications, including delayed wound healing, hematoma, seroma, and infection were captured. Additionally, adverse events, defined as a documented allergic reaction that occurred in either experimental arm were collected.

The main outcomes of interest included pain scores, sleep scores, and measures of anxiety and depression. Secondary outcomes of interest included an analysis of how blood pressure, heart rate, and respiratory rate were influenced by lavender oil in the perioperative period. Pain scores were captured using the visual analogue scale and recorded on a scale of 1 to 10.[23] Sleep scores were measured using the Richards–Campbell Sleep Questionnaire.[24] This is a brief 6-item questionnaire where a total score is calculated to represent the overall quality of a person's sleep, with higher scores representing better sleep. The Hospital Anxiety and Depression Scale (HADS) was used to quantify levels of anxiety and depression.[25] This 14-component scoring system is used to tabulate a total sum score (0–42) or separate anxiety and depression scores (0–21). A higher score represents a more severe degree of anxiety and/or depression. The severity of a patient's anxiety or depression may then be grouped into three categories based on the score (normal, 0–7; borderline abnormal, 8–10; and abnormal 11–21).

Statistical Analysis

Categorical variables were summarized using frequency and percentage and compared using Fisher's exact tests. Continuous variables were summarized with median, interquartile range (IQR), and compared using Wilcoxon's rank sum tests. Linear mixed-effect models were used to investigate HADS (total, anxiety, and depression), sleep, and pain scores. Variables for time point (preoperative/POD1/final POD) and arm were analyzed while adjusted for the patient's reconstruction laterality. First the interaction of time point by study arm was tested. If the interaction was nonsignificant, it was dropped from the model before testing the main effects for time and arm. The underlying covariance structure used for all mixed models was unstructured and estimation was based on the restricted maximum likelihood method. Adjustment for multiple pairwise comparisons used the Scheffe method. Analyses were conducted based on the intent to treat principle. p-Values of <0.05 were considered statistically significant. Line plots illustrate changes in vital signs over time. At each time point, the mean and corresponding 95% confidence interval has been plotted. All analyses were conducted using SAS software (Version 9.4; SAS Institute Inc., Cary, NC), and plots were created in the R language and environment for statistical computing (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline Characteristics of Study Population

From December 2017 to January 2020, 58 patients were enrolled in this study. Nine patients (two in the experimental group and seven in the control group) were excluded from final analysis after withdrawing from the study or due to incomplete data and/or medical records. The baseline characteristics of the study cohort are in ►**Table 1**. The median age was 47.6 years (range, 32–68 years). The two study groups were similar with respect to BMI, race, smoking status, medical comorbidities, and presence of past psychiatric history (including anxiety and depression). Most patients underwent a delayed (46.9%, $n = 23$) form of microvascular breast reconstruction, received bilateral reconstruction (57.1%, $n = 28$), and received a deep inferior epigastric artery perforator flap (55.1%, $n = 27$). Reconstruction laterality was the only variable that varied significantly between the experimental and control groups with a larger number of patients in the experimental group undergoing unilateral breast reconstruction (59.3%, $n = 16$ vs. 22.7%, $n = 5$; $p = 0.02$).

Hospital Anxiety and Depression Scores

Summary results regarding the effects of lavender oil on HADS anxiety and depression scores are shown in ►**Table 2**. HADS anxiety scores revealed that the mean preoperative, POD1, and final POD scores for all patients were 9.4 (standard deviation

Table 1 Patient characteristics

	Placebo/control ($n = 22$) *n* (%)	Experimental ($n = 27$) *n* (%)	Total ($n = 49$) *n* (%)	*p*-Value
Age at surgery (y)				
n	22	27	50	0.7938[a]
Median (IQR)	46.7 (40.6–54.9)	48.2 (41.9–56.0)	47.6 (41.1–54.9)	
Range	31.6–67.5	31.8–66.9	31.6–67.5	
BMI				
n	22	27	49	0.6152[a]
Median (IQR)	27.8 (25.5–31.8)	27.9 (24.4–30.4)	27.9 (24.7–30.7)	
Range	20.9–40.1	19.6–36.0	19.6–40.1	
Time elapsed between date of diagnosis and date of reconstruction? (mo)				
n	21	26	47	0.7891[a]
Median (IQR)	21.6 (14.1–112.5)	20.0 (14.8–33.1)	20.0 (14.4–47.2)	
Range	3.3–274.6	2.1–218.1	2.1–274.6	
Race				
Asian	2 (9.1)	0 (0.0)	2 (4.0)	
Black or African American	2 (9.1)	5 (17.9)	7 (14.0)	
White	12 (54.5)	20 (71.4)	32 (64.0)	
Multiracial	3 (13.6)	0 (0.0)	3 (6.0)	
Other	1 (4.5)	0 (0.0)	1 (2.0)	
Unavailable	2 (9.1	3 (10.7)	5 (10.0)	
Smoker, current or former	6 (27.3)	10 (38.5)	16 (33.3)	0.5421[b]
Medical comorbidities				
Hypertension	4 (18.2)	6 (21.4)	10 (20.0)	1.0000[b]
Diabetes	1 (4.5)	1 (3.6)	2 (4.0)	1.0000[b]
Hyperlipidemia	1 (4.5)	1 (3.6)	2 (4.0)	1.0000[b]
Chronic pain disorder	2 (9.1)	3 (11.5)	5 (10.4)	1.0000[b]
Documented psychiatric history	9 (40.9)	13 (50.0)	22 (45.8)	0.5729[b]
Psychiatric illnesses				
Anxiety	7 (31.8)	9 (32.1)	16 (32.0)	1.0000[b]
Depression	4 (18.2)	8 (28.6)	12 (24.0)	0.5116[b]
Other	1 (4.5)	0 (0.0)	1 (2.0)	0.4400[b]
Breast surgery history				
Simple mastectomy	17 (77.3)	23 (82.1)	40 (80.0)	0.7317[b]
Nipple sparing mastectomy	2 (9.1)	3 (10.7)	5 (10.0)	1.0000[b]
Sentinel lymph node biopsy	11 (50.0)	11 (39.3)	22 (44.0)	0.5685[b]
Axillary lymph node dissection	7 (31.8)	12 (42.9)	19 (38.0)	0.5595[b]
Lumpectomy	3 (13.6)	1 (3.6)	4 (8.0)	0.3136[b]
Breast cancer type				
DCIS	5 (22.7)	3 (10.7)	8 (16.0)	0.2770[b]
Invasive	17 (77.3)	22 (78.6)	39 (78.0)	1.0000[b]
Not documented	1 (4.5)	0 (0.0)	1 (2.0)	0.4400[b]
Hormone receptor status				
ER+	15 (68.2)	17 (60.7)	32 (64.0	0.7676[b]
PR+	10 (45.5)	17 (60.7)	27 (54.0)	0.3926[b]
Her2+	7 (31.8)	4 (14.3)	11 (22.0)	0.1781[b]

Table 1 (*Continued*)

	Placebo/control ($n=22$) *n* (%)	Experimental ($n=27$) *n* (%)	Total ($n=49$) *n* (%)	*p*-Value
Radiation therapy	13 (59.1)	20 (74.1)	33 (67.3)	0.3612[b]
Chemotherapy	16 (72.7)	20 (74.1)	36 (73.5)	1.0000[b]
Chemotherapy timing				
Neoadjuvant	6 (27.3)	10 (35.7)	16 (32.0)	0.5589[b]
Adjuvant	10 (45.5)	9 (32.1)	19 (38.0)	0.3888[b]
Other	0 (0.0)	1 (3.6)	1 (2.0)	1.0000[b]
Hormonal therapy	14 (66.7)	19 (70.4)	33 (68.8)	1.0000[b]
Documented psychiatric history	9 (40.9)	13 (50.0)	22 (45.8)	0.5729[b]
Psychiatric illnesses				
Anxiety	7 (31.8)	9 (32.1)	16 (32.0)	1.0000[b]
Depression	4 (18.2)	8 (28.6)	12 (24.0)	0.5116[b]
Other	1 (4.5)	0 (0.0)	1 (2.0)	0.4400[b]
Reconstruction type				
Unilateral	5 (22.7)	16 (59.3)	21 (42.9)	0.0193[b]
Bilateral	17 (77.3)	11 (40.7)	28 (57.1)	
Contralateral prophylactic reconstruction	16 (72.7)	12 (44.4)	28 (57.1)	0.0808[b]
Type of free flap				
Unilateral DIEP	3 (13.6)	2 (7.4)	5 (10.2)	
Bilateral DIEP	16 (72.7)	11 (40.7)	27 (55.1)	
Stacked DIEP	2 (9.1)	13 (48.1)	15 (30.6)	
Other	1 (4.5)	1 (3.7)	2 (4.1)	

Abbreviations: BMI, body mass index; DCIS, ductal carcinoma in situ; DIEP, deep inferior epigastric artery perforator; ER, estrogen receptor; HER2, human epidermal growth factor 2; IQR, interquartile range; PR, progesterone receptor.
[a]Wilcoxon's rank sum *p*-value.
[b]Fisher's exact *p*-value.

[SD] ± 3.62), 7 (SD ± 3.49), and 6.9 (SD ± 3.16), respectively. Preoperatively, 36.6% ($n=15$), 24.4% ($n=10$), and 39% ($n=16$) of patients were classified as "normal," "borderline abnormal," and "abnormal" based on the anxiety scores, respectively. At the time of the final postoperative survey, 59% ($n=23$), 28.2% ($n=11$), and 12.8% ($n=5$) of patients were classified as "normal," "borderline abnormal," and "abnormal" based on the anxiety scores, respectively. HADS depression scores revealed that the mean preoperative, POD1, and final POD scores for all patients was 14.6 (SD ± 1.73), 14.9 (SD ± 2.55), and 15.7 (SD ± 1.94), respectively. Preoperatively, 4.9% ($n=2$), and 97.5% ($n=39$) of patients were classified as "borderline abnormal" or "abnormal," respectively, based on the depression scores. At the time of the final postoperative survey, 2.6% ($n=1$) and 97.4% ($n=38$) of patients were classified as "borderline abnormal" and "abnormal," respectively, based on the depression scores.

Mixed linear-effect models tested the interaction of the randomization arm and time point on all scores. No significant interaction effects were observed. Next, the main effects for arm and time were tested. Overall, no significant differences were found based on randomization into the experimental or control groups when comparing total HADS ($p=0.36$), HADS anxiety ($p=0.82$), or HADS depression scores ($p=0.21$; ►**Table 3**). However, when considering the total patient cohort, significant differences in HADS scores were seen based on time ($p<0.01$). Notably, HADS anxiety scores were found to be significantly lower in the postoperative period as compared with preoperative scores ($p<0.001$), while HADS depression scores were found to be significantly higher in the postoperative period as compared with the preoperative period ($p=0.005$; ►**Table 4**; ►**Fig. 2**). This suggests that patients may experience lessened anxiety but increased symptoms of depression in the immediate postoperative period following microvascular breast reconstruction.

Sleep Scores, Pain Scores, and Vital Signs

Outcomes regarding sleep and pain scores are summarized in ►**Table 2**. Mean preoperative, POD1, and final POD sleep scores were 6.0 (SD ± 2.49), 5.3 (SD ± 2.02), and 7.1 (SD ± 2.04), respectively. Mean preoperative, POD1, and final POD pain scores were 0.7 (SD ± 1.62), 3.3 (SD ± 2.43), and 2.7 (SD ± 2.48), respectively. Overall, no significant differences were seen between the arms for sleep ($p=0.86$) or pain ($p=0.30$) scores (►**Table 3**). However, when considering the total patient cohort, significant differences in sleep and pain scores were seen based on time. In general, patients demonstrated improved sleep scores ($p=0.021$) and improved pain scores

Table 2 Summary results for outcomes

	Placebo/control ($n = 22$)	Experimental ($n = 27$)
Total HADS, preoperative		
n	17	24
Mean (SD)	10.9 (7.07)	11.9 (7.32)
Median (IQR)	10.0 (7.0–14.0)	10.0 (7.0–16.0)
Range	0.0–28.0	3.0–30.0
Total HADS, POD1		
n	16	24
Mean (SD)	9.9 (5.65)	10.3 (7.79)
Median (IQR)	9.5 (6.5–13.5)	9.0 (4.0–14.0)
Range	0.0–21.0	2.0–39.0
Total HADS, final POD		
n	16	23
Mean (SD)	9.4 (6.21)	8.0 (5.40)
Median (IQR)	9.5 (4.5–12.5)	6.0 (4.0–12.0)
Range	1.0–24.0	0.0–19.0
HADS anxiety, preoperative		
n	17	24
Mean (SD)	9.6 (4.40)	9.2 (3.03)
Median (IQR)	10.0 (6.0–11.0)	9.0 (7.0–12.0)
Range	3.0–21.0	4.0–15.0
HADS anxiety, preoperative *n* (%)		
0–7: normal	5 (29.4)	10 (41.7)
8–10: borderline abnormal	5 (29.4)	5 (20.8)
11–21: abnormal	7 (41.2	9 (37.5)
HADS anxiety, POD1		
n	16	24
Mean (SD)	7.6 (3.65)	6.5 (3.40)
Median (IQR)	7.0 (4.0–11.0)	6.0 (4.0–8.0)
Range	3.0–13.0	2.0–16.0
HADS anxiety, final POD		
n	16	23
Mean (SD)	7.7 (3.52)	6.3 (2.82)
Median (IQR)	7.0 (5.0–9.5)	6.0 (4.0–8.0)
Range	3.0–16.0	2.0–12.0
HADS anxiety, final POD *n* (%)		
0–7: normal	9 (56.3)	14 (60.9)
8–10: borderline abnormal	4 (25.0	7 (30.4)
11–21: abnormal	3 (18.8)	2 (8.7)

Table 2 (*Continued*)

	Placebo/control ($n = 22$)	Experimental ($n = 27$)
HADS depression, preoperative		
n	17	24
Mean (SD)	14.9 (1.68)	14.4 (1.77)
Median (IQR)	15.0 (14.0–16.0)	15.0 (14.0–16.0)
Range	12.0–18.0	10.0–16.0
HADS depression, preoperative *n* (%)		
8–10: borderline abnormal	0 (0.0)	2 (8.3)
11–21: abnormal	17 (100.0)	22 (91.7)
HADS depression, POD1		
n	16	24
Mean (SD)	14.8 (2.14)	15.0 (2.84)
Median (IQR)	14.0 (13.5–16.5)	16.0 (13.0–16.5)
Range	11.0–18.0	7.0–19.0
HADS depression, final POD		
n	16	23
Mean (SD)	15.8 (2.77)	15.7 (1.11)
Median (IQR)	15.5 (14.0–17.5)	16.0 (15.0–16.0)
Range	10.0–21.0	14.0–18.0
HADS depression, final POD *n* (%)		
8–10: borderline abnormal	1 (6.3)	0 (0.0)
11–21: abnormal	15 (93.8)	23 (100.0)
Sleep scores, preoperative		
n	17	24
Mean (SD)	6.5 (2.61)	5.6 (2.39)
Median (IQR)	6.5 (4.2–8.3)	5.3 (3.8–7.7)
Range	1.3–10.0	1.7–10.0
Sleep scores, POD1		
n	16	24
Mean (SD)	5.5 (1.97)	5.1 (2.08)
Median (IQR)	5.7 (4.3–7.2)	5.7 (3.2–6.3)
Range	1.5–8.3	1.8–9.2
Sleep scores, final POD		
n	16	23
Mean (SD)	6.6 (2.43)	7.4 (1.71)
Median (IQR)	6.8 (4.5–8.9)	7.8 (5.8–8.7)
Range	2.7–10.0	3.5–10.0

Table 2 (*Continued*)

	Placebo/control ($n = 22$)	Experimental ($n = 27$)
Pain score, preoperative		
n	18	24
Mean (SD)	0.5 (1.36)	0.9 (1.80)
Median (IQR)	0.0 (0.0–0.0)	0.0 (0.0–0.5)
Range	0.0–5.5	0.0–5.0
Pain score, POD1		
n	14	22
Mean (SD)	3.5 (1.91)	3.1 (2.74)
Median (IQR)	4.0 (2.0–4.7)	2.6 (1.2–4.5)
Range	0.0–6.0	0.0–9.0
Pain score, final POD		
n	15	23
Mean (SD)	2.5 (1.92)	2.9 (2.81)
Median (IQR)	2.2 (0.6–4.0)	2.3 (0.0–5.0)
Range	0.0––6.0	0.0–9.0

Abbreviations: HADS, hospital anxiety and depression scale; IQR, interquartile range; POD, postoperative day; SD, standard deviation.

Table 3 Mixed-model results

Outcome	Effect	*p*-Value
HADS total scores	Arm × time	ns
	Arm	0.3589
	Time	0.0004
HADS anxiety scores	Arm × time	ns
	Arm	0.8163
	Time	<0.0001
HADS depression scores	Arm × time	ns
	Arm	0.2069
	Time	0.0131
Sleep scores	Arm × time	ns
	Arm	0.8585
	Time	<0.0001
Pain scores	Arm × time	ns
	Arm	0.3002
	Time	<0.0001

Abbreviations: HADS, hospital anxiety and depression scale; ns, nonsignificant then dropped from model before testing main effects.

throughout the length of their hospitalization ($p < 0.001$; ►**Table 4**; ►**Fig. 2**).

The physiologic effect of lavender oil on respiration rate, heart rate, systolic blood pressure, and diastolic blood pressure was measured in the preoperative and postoperative period and compared between groups. No significant differences were seen at any of the measured time points (►**Fig. 3**). In addition, no significant differences in the rates delayed wound

Table 4 Pairwise comparisons

Score	Pairwise comparison	Scheffe's *p*-value
HADS total	Pre-op and POD1 Pre-op and final POD[a] POD1 and final POD[a]	0.13 <0.001 0.036
HADS anxiety	Pre-op and POD1[a] Pre-op and final POD[a] POD1 and final POD	<0.001 <0.001 0.94
HADS depression	Pre-op and POD1 Pre-op and final POD[a] POD1 and final POD	0.48 0.005 0.052
Sleep score	Pre-op and POD1 Pre-op and final POD[a] POD1 and final POD[a]	0.082 0.021 <0.001
Pain score	Pre-op and POD1[a] Pre-op and final POD[a] POD1 and final POD	<0.001 <0.001 0.14

Abbreviations: HADS, hospital anxiety and depression scale; POD, postoperative day; Pre-op, preoperative.
[a]Indicates a pairwise comparison with adjusted $p < 0.05$.

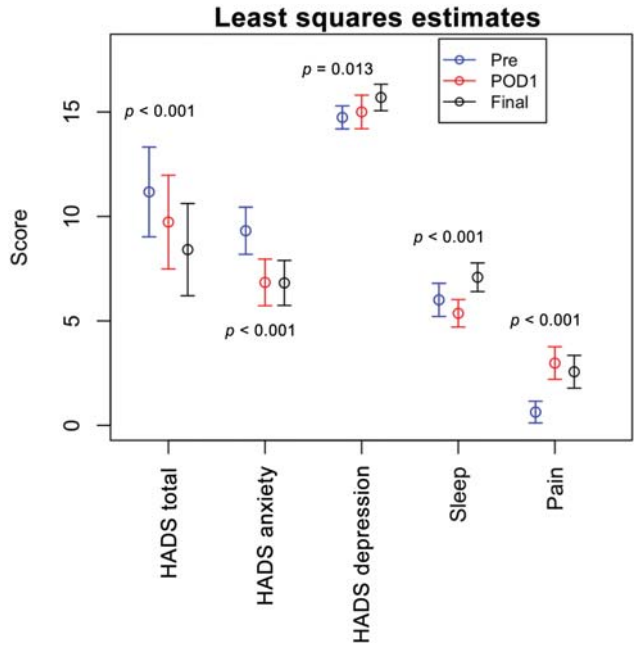

Fig. 2 Least squares mean estimates and 95% confidence intervals obtained for the total patient cohort from the linear mixed models: *p*-values are from mixed model test of main effect for time. HADS, hospital anxiety and depression scale; POD, postoperative day.

healing (22.7 vs. 21.4%; $p = 1.00$), hematoma (4.5 vs. 17.9%; $p = 0.21$), seroma (4.5 vs. 14.3%; $p = 0.37$), infection (22.7 vs. 32.1%; $p = 0.54$), or flap congestion (4.5 vs. 0%; $p = 0.44$) were seen, and no adverse events related to the essential oil were documented throughout the trial (►**Table 5**).

Discussion

To our knowledge, this is the first randomized controlled trial to directly assess the therapeutic benefits of lavender oil to alleviate perioperative pain, anxiety, depression, and improve

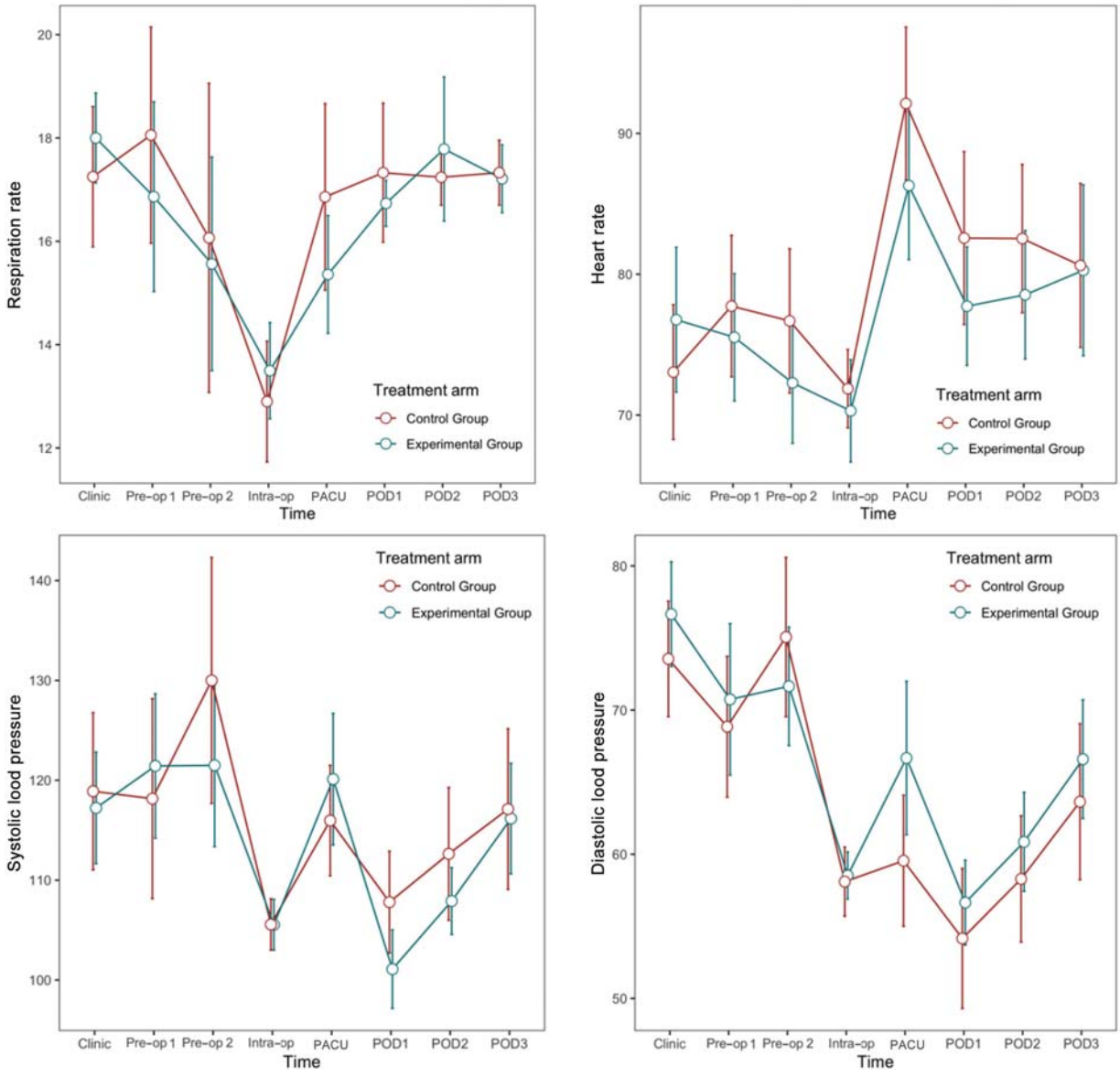

Fig. 3 Trends of vital signs over time before and after essential oil application in the treatment arms. Time points represented are (1) clinic visit, (2) preoperative before lavender administration, (3) preoperative after lavender administration, (4) intraoperative, (5) PACU, (6) postoperative day (POD) 1, (7) POD2, and (8) POD3. PACU, post anesthesia care unit.

Table 5 Complications by arm

	Placebo/control ($n = 22$)	Experimental ($n = 27$)	Total ($n = 49$)	p-Value
Surgical complication *n* (%)				
No	9 (45.0)	11 (44.0)	20 (44.4)	1.0000[a]
Yes	11 (55.0)	14 (56.0)	25 (55.6)	
Surgical complications *n* (%)				
Delayed wound healing	5 (22.7)	6 (21.4)	11 (22.0)	1.0000[a]
Hematoma	1 (4.5)	5 (17.9)	6 (12.0)	0.2109[a]
Seroma	1 (4.5)	4 (14.3)	5 (10.0)	0.3681[a]
Infection	5 (22.7)	9 (32.1)	14 (28.0)	0.5374[a]
Flap congestion	1 (4.5)	0 (0.0)	1 (2.0)	0.4400[a]

[a]Fisher's exact p-value.

sleep in patients undergoing microvascular breast reconstruction. The results of this study suggest that there are no significant differences in HADS anxiety or depression scores, pain scores, sleep scores, or vital signs when comparing patients who received lavender oil and the control group who received coconut oil. In addition, the application of lavender oil did not result in an increased incidence of adverse events or surgical-related complications when compared with the control group. Overall, the results of this study suggest that lavender oil may be safely used as an adjunct in patients undergoing microvascular breast reconstruction as part of multimodal analgesic treatment; however, it should not be used as a sole therapy to treat anxiety, depression, sleeplessness, or perioperative pain.

Linalool and linalyl acetate are chemical constituents of lavender that are believed to contribute to its therapeutic effect through inhibition of GABA(A) receptors in the central nervous system to induce a state of relaxation and mitigate pain perception.[14,15] This proposed mechanism has also been suggested to reduce physiological stress responses and trigger reductions in blood pressure and heart rate.[26,27] The results of our study suggest that there are no meaningful differences in blood pressure or heart rate when comparing the vital signs of patients who receive lavender oil and those in the control group. However, further research is needed to elucidate the potential physiological effects of inhaled lavender oil on the surgical patient.

Prior studies examining the therapeutic benefit of aromatherapy and lavender oil have presented conflicting results. Essential oils have been suggested to reduce perioperative anxiety and pain in patients admitted to intensive care units and those awaiting ambulatory surgery, in addition to patients undergoing cesarean sections and coronary artery bypass grafting.[11,12,16,19–21,28–32] Specifically, Olapour et al reported that among patients undergoing a cesarean section, those who received lavender oil as part of their multimodal pain regimen demonstrated less postoperative pain and improved satisfaction with pain control.[32] However, the authors emphasize in this study that while lavender oil appears to be safe and demonstrates a therapeutic effect, it should not be used as a sole measure for pain management. In contrary, Kim et al reported on the analgesic effects of lavender oil in patients undergoing a breast biopsy, finding that there was no objective difference in patient-reported pain scores. However, patients' who received lavender oil reported improved satisfaction with their pain control.[33] Salamati et al demonstrated similar findings when assessing the benefits of lavender oil in patients undergoing open-heart surgery, found that lavender oil did not confer an objective, measurable benefit with pain control.[21] Our results support these findings and suggest that while lavender aromatherapy may not display a direct analgesic or mood stabilizing effect, it does provide a low-cost and safe adjunct that has the potential to positively impact a patient's subjective perception of their treatment-related pain.[34] It should be noted, however, that the utilization of an ERAS pathway may have influenced the results of this study. The use of ERAS pathways in microvascular breast reconstruction have been shown to reduce opioid use and improve pain control as compared with traditional postsurgical pathways.[35,36] It is unclear if the effects of lavender aromatherapy may be more pronounced in the absence of the perioperative multimodal pain regimens seen in conjunction with ERAS pathways.

While no meaningful difference existed with respect to the severity of HADS depression and anxiety scores, interesting trends were observed when examining the total patient cohort. In general, breast reconstruction patients were found to display a reduction in their HADS anxiety scores prior to discharge. However, HADS depression scores persisted in the "borderline abnormal" to "abnormal" range signifying the pervasiveness of mental health issues, like depression, throughout the perioperative period of breast reconstruction. These results are like previous studies examining the long-term psychosocial outcomes associated with breast reconstruction.[2–4] Metcalfe et al reported on the psychosocial functioning of women diagnosed with breast cancer, found that breast reconstruction patients demonstrated improved psychosocial scores over time with relatively low levels of distress and depression over a 6-year period.[2] However, the authors note that a significant portion of women continue to experience moderate-to-severe cancer-related distress which is especially notable among patients who undergo a form of delayed breast reconstruction.[2] Women who undergo mastectomy, with or without breast reconstruction, tend to experience heightened psychosocial distress in the acute perioperative period following a cancer diagnoses and surgery. This may be attributed to concerns regarding a patient's postmastectomy appearance and factors such as a lower household income, lack of social support, higher tumor stage, and a history of depression and/or anxiety.[37–40] Patients may be at the highest risk for anxiety and depression during first year after a cancer diagnoses. This may be related to a fear of recurrence, loss of social support, and fatigue and pain after surgery which prevents a return to normal daily activities.[41] Previous studies note, however, that psychosocial distress related to a breast cancer diagnoses or surgery tends to resolve overtime and does not appear to have a long-standing effect on patient wellbeing.[42,43] Our study population was largely composed of women who underwent a form of delayed breast reconstruction which may account for the high level of depression seen in this cohort. It is important for reconstructive surgeons to recognize that patients seeking breast reconstruction may have higher baseline levels of cancer-related distress and should be ready to offer the appropriate avenues for support and counseling when needed.

Limitations

We acknowledge several limitations. The study sample size was not calculated a priori but was chosen arbitrarily. This is the first study designed to evaluate the use of lavender oil in breast reconstruction patients and thus a power analysis could not be performed with a degree of confidence. Therefore, a type-II error cannot be ruled out as the statistical power of this study may limit our conclusions. Most of the hospital discharges took place on POD3 or POD4, and this length of follow-up time may not have been adequate to

observe an effect between the patient groups. Additionally, complications experienced by patients may have affected perceptions of pain, anxiety, depression, and sleep. However, due to the low incidence of complications in this cohort, the independent effect of postoperative complications on individual scores could not be assessed. In addition, we did not capture a baseline incidence of sleep disturbance in our patient cohort, and variations in a patient's baseline emotional state, pain tolerance, and the effect of standard postoperative pharmacologic agents on lavender essential oil were not controlled in this study. Lastly, while this trial was blinded to the patient, the distinct scent of the lavender oil makes it difficult to utilize a placebo in this study.

Conclusion

We hypothesized that in patients undergoing microvascular breast reconstruction, topical and aromatherapy with lavender oil would result in objective improvements in perioperative pain, anxiety, depression, and sleep. However, the results of this study suggest that lavender oil does not confer measurable advantages when used as an adjunct to multimodal pain regimens. Despite this, lavender oil is a low-cost therapeutic that may be safely used in the postoperative management of the breast reconstruction patient. Further investigation into the potential role of aromatherapy in patients undergoing breast reconstruction is warranted.

Note

This study is registered with ClinicalTrials.gov with identifier no. NCT03093454. An investigational new drug application was filed with the United States Food and Drug Administration for this study.

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Conflict of Interest

None declared.

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